Hepatitis A Virus Infections

Robert L. Brawley, MD, MPH, FSHEA
Chief, Infectious Disease Branch
Division of Epidemiology and Health Planning
Kentucky Department for Public Health

Kentucky Public Health
Prevent. Promote. Protect.

Kentucky
UNBRIDLED SPIRIT

Objectives

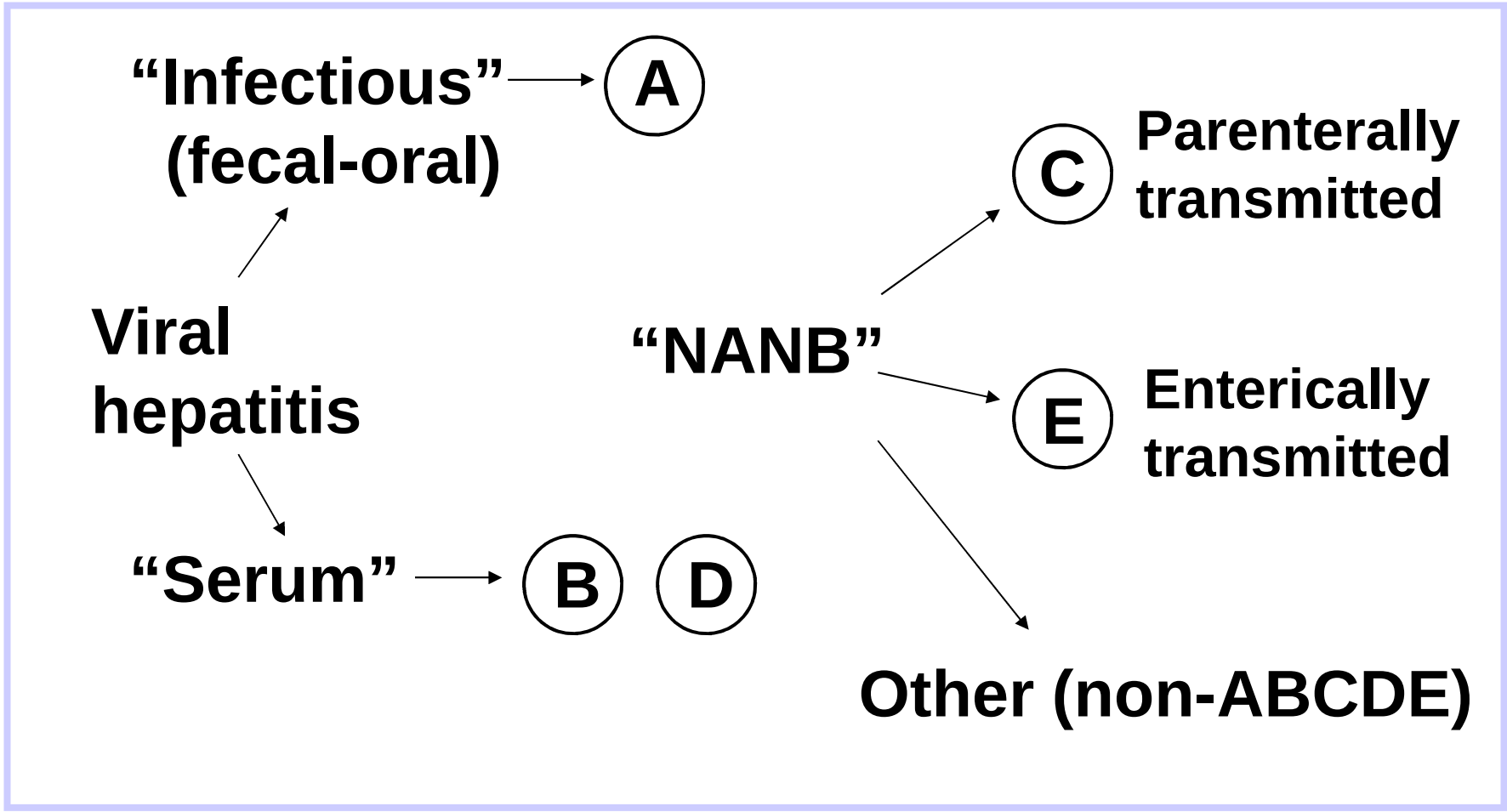
- Discuss the pathogenesis and epidemiology of hepatitis A virus (HAV) infections
- Discuss clinical features of HAV infections
- Discuss the risk factors for HAV infections
- Discuss methods to prevent HAV infections

Kentucky
UNBRIDLED SPIRIT

Hepatitis A – History Tidbits

- Epidemic jaundice described by Hippocrates, as early as 400 BC
- Further outbreaks of jaundice in 17th and 18th Century Europe, associated with conflicts
- Earliest recorded US outbreak, Norfolk, VA 1812
- HAV likely was one of the causes of “camp jaundice” or “field jaundice” in wartimes
- **Krugman differentiated “infectious” hepatitis from “serum” hepatitis in 1967**
- Serologic tests developed in 1970s
- Vaccines licensed in 1995 and 1996

Viral Hepatitis – Historical Epi Perspective

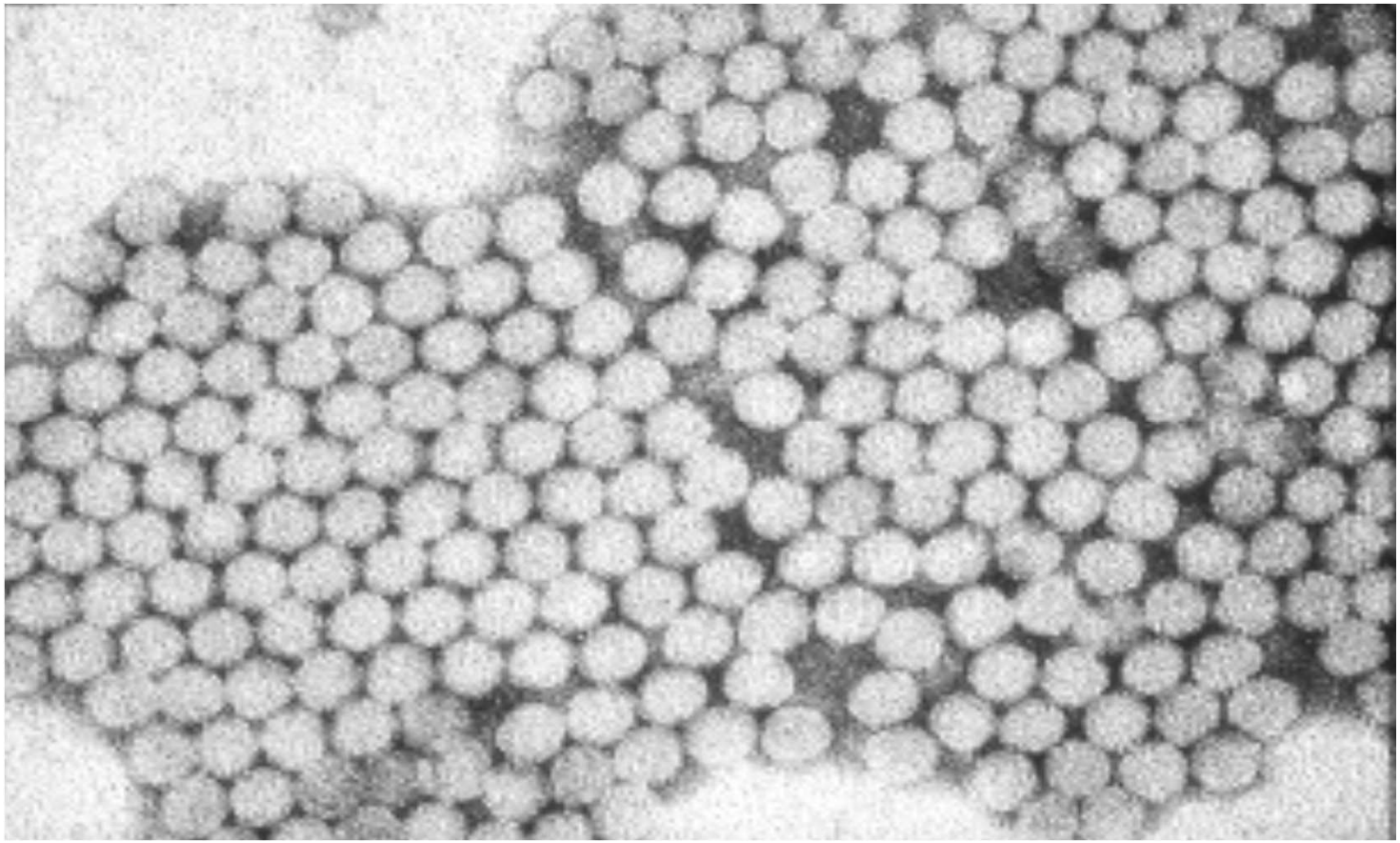


Kentucky UNBRIDLED SPIRIT

Hepatitis A Virus (HAV)

- Picornavirus (RNA), 27-32 nm in diameter
- Spherical with icosahedral symmetry
- 1 serotype and 6 genotypes. Genotypes I, II, and III, with subtypes A & B infect humans. Genotype IIIA may cause more severe disease.
- **Humans and non-human primates are natural hosts**
- Stable at low pH (pH 1 for 2 hours)
- Inactivated by high temperature (≥185°F), formalin, chlorine, autoclaving (250°F – 30 min)
- **Complete inactivation in food, e.g., shellfish, requires heating to ≥185°F for at least one minute**
- **May survive days to weeks in shellfish, soil, water, or marine sediment**

Hepatitis A Virus



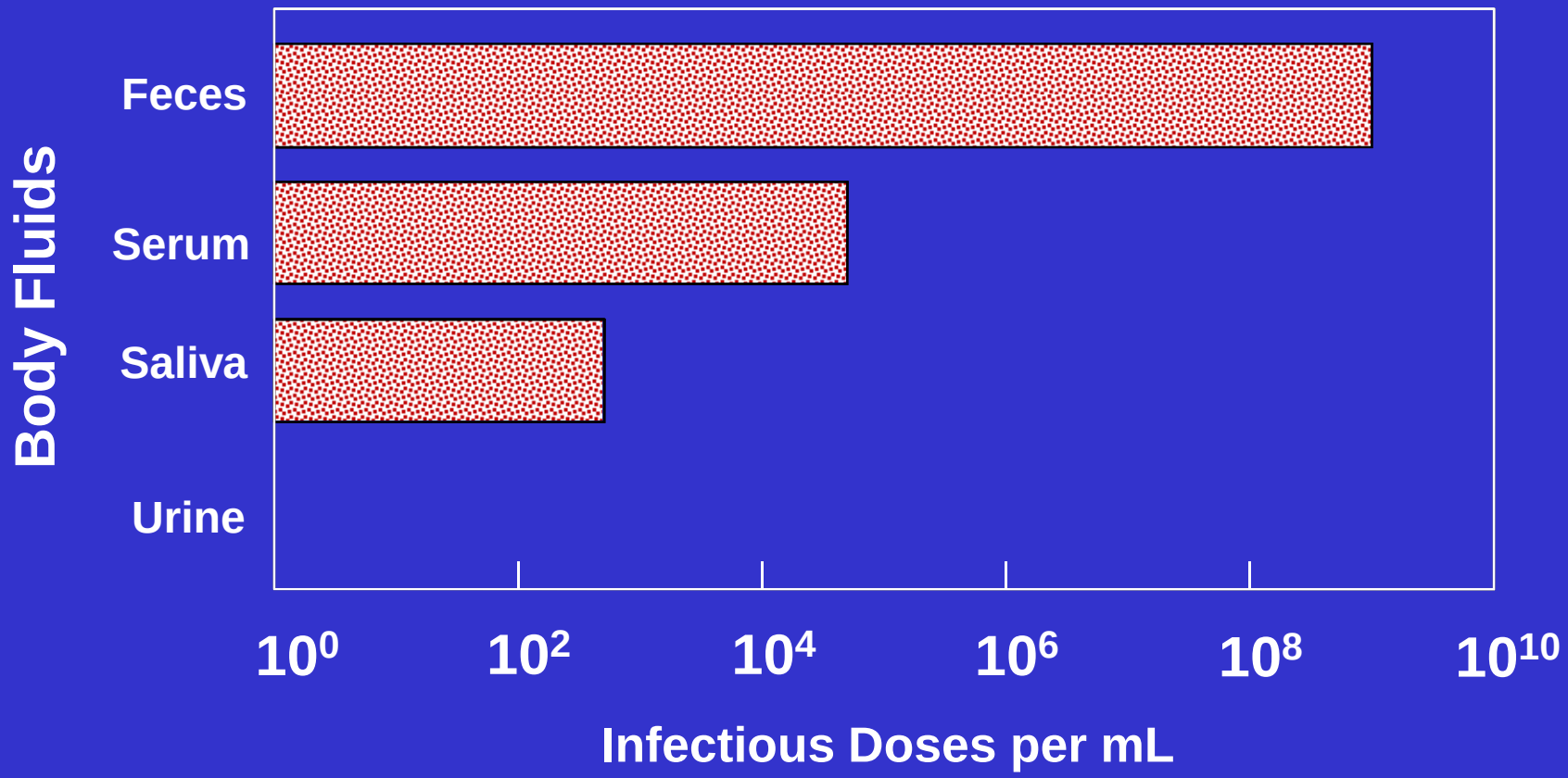
Electron micrograph of Hepatitis A virus

Hepatitis A Pathogenesis

- Entry into the mouth (fecal-oral transmission is the most common mode of HAV transmission)
- Acid resistant virus, passes through stomach to intestines
- Transport to liver, major site of viral replication
- Virus present in liver, bile, blood, and feces 10-12 days after infection
- Virus excretion may continue for up to 3 weeks after onset of symptoms. Virus excretion can extend up to six months in infected neonates.
- Period of infectivity, e.g., one week after jaundice appears, is shorter than duration of HAV RNA in stool

Kentucky Public Health
Prevent. Promote. Protect.

Concentration of Hepatitis A Virus in Various Body Fluids



Source: Viral Hepatitis and Liver Disease 1984;9-22
J Infect Dis 1989;160:887-890

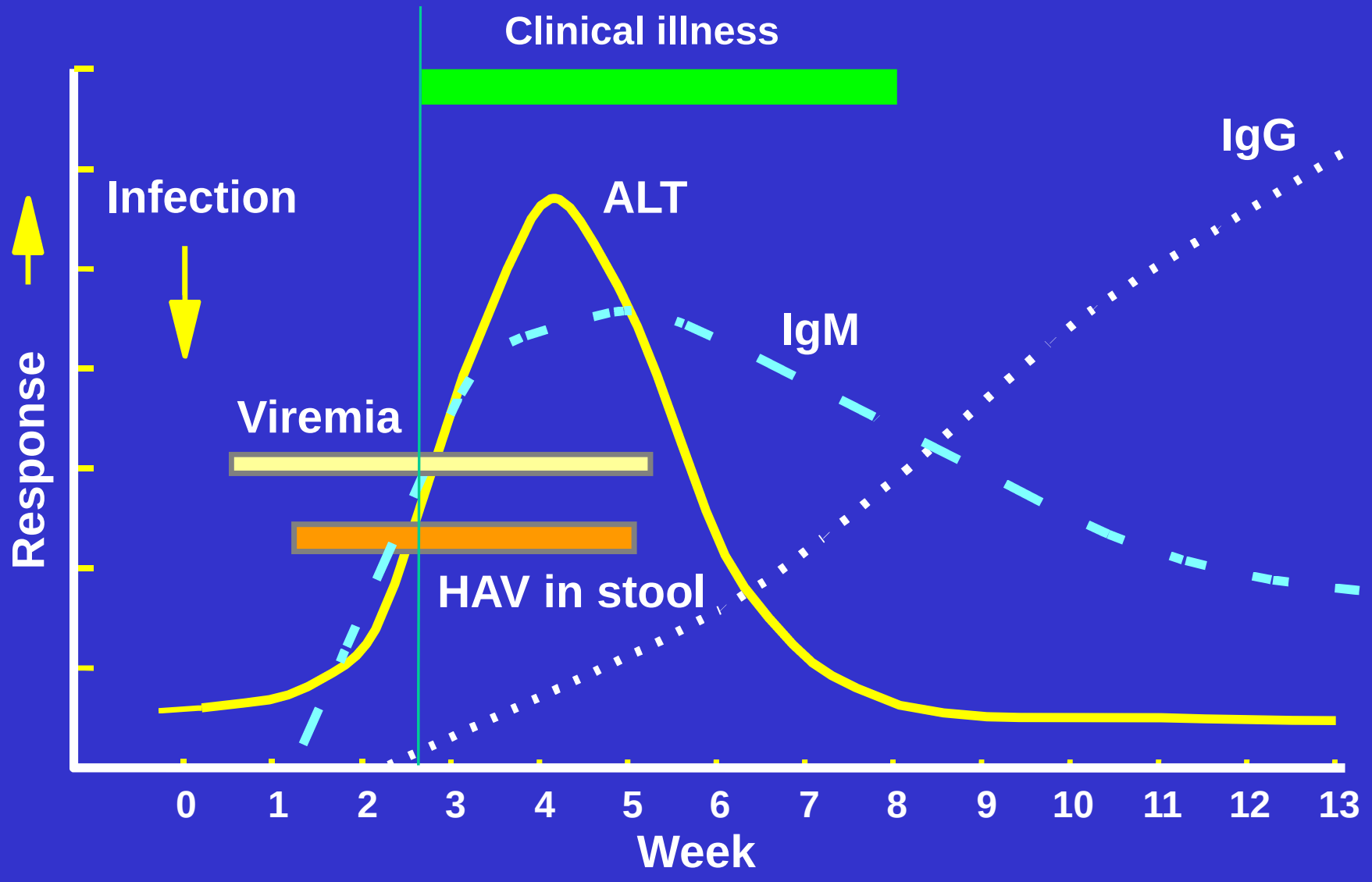
Cabinet for Health and Family Services

Acute Hepatitis A - Clinical Features

- Incubation period averages 28 - 30 days (range 15 - 50 days)
- Illness not specific for hepatitis A
- Hepatitis A virus excreted in feces for 1-2 weeks before onset and for at least one week after onset
- Likelihood of symptomatic illness and hospitalization directly related to age
  - Children generally asymptomatic, adults symptomatic
- **No chronic infection from HAV**
  - Protective antibodies develop in response to acute hepatitis A infection and confer lifelong immunity

Kentucky Public Health
Prevent. Promote. Protect.

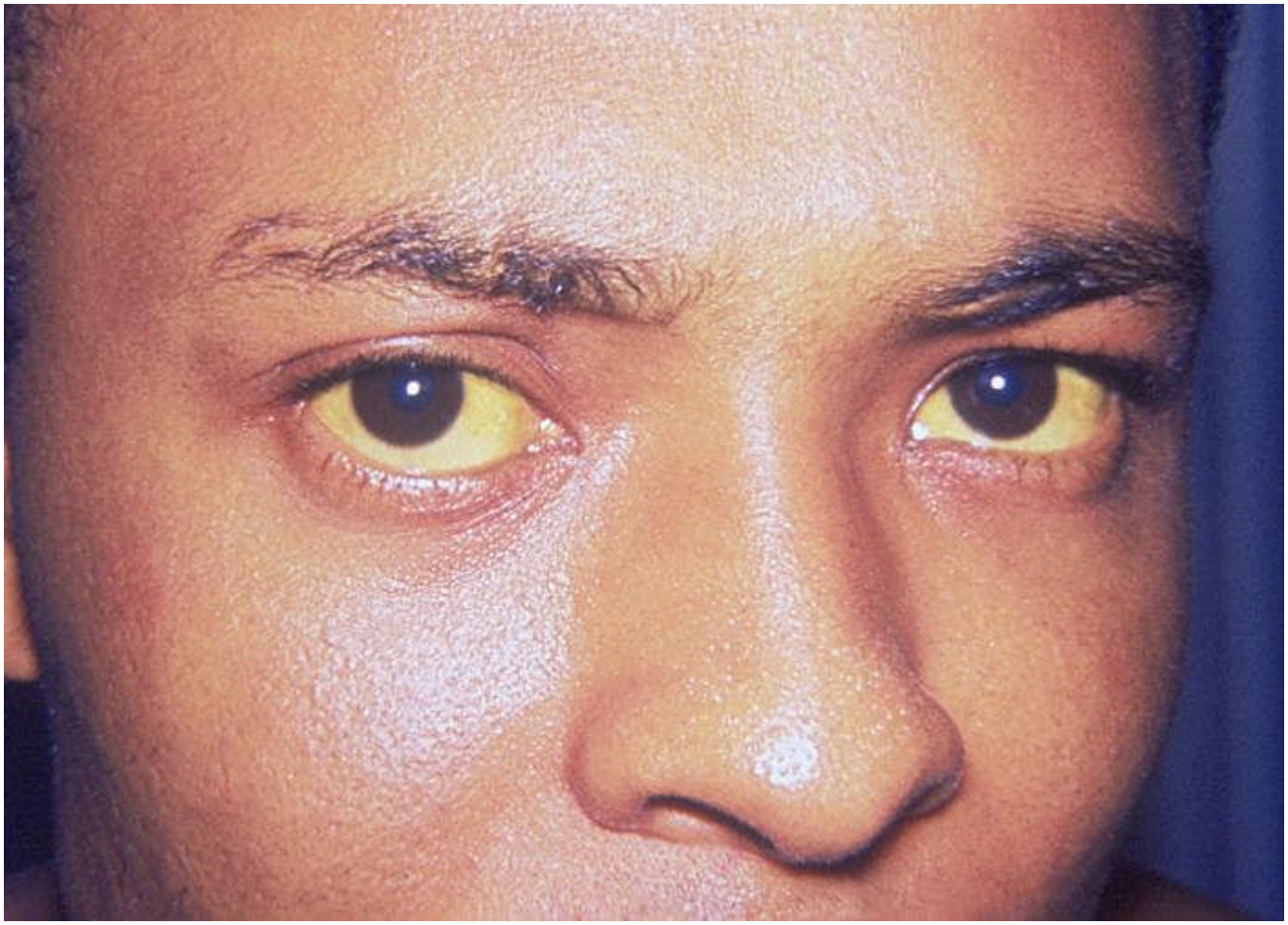
Events In Hepatitis A Virus Infection



Acute Hepatitis – Clinical Symptoms

- Asymptomatic infections > Symptomatic diseases > Fulminant Liver Failure > Death
- Symptoms (if present) are similar, regardless of cause (e.g., A, B, C, other viruses, toxins)
  - Fever
  - Nausea, vomiting
  - Loss of appetite
  - Abdominal pain
  - Dark urine
  - Jaundice (yellowing of eyes, skin)
  - Light (clay) colored stools
  - Diarrhea (more common in children with hepatitis A)

Jaundice



Acute Hepatitis A

- Symptoms
  - Jaundice 84%
  - Weight loss 82%
  - Malaise 80%
  - Fever 76%
  - Nausea 69%
  - Vomiting 47%
  - Abd pain 37%
  - Arthralgias 6%
- Clinical Findings
  - Hepatomegaly 87%
  - Splenomegaly 9%
  - Skin rashes 3%
  - Mild edema 2%
  - Petechiae 2%
  - Cardiac arrhythmias <1%

1988 Shanghai epidemic, 8647 hospitalized patients

Acute Hepatitis A

- Symptoms
  - Dark urine 68-94%
  - Anorexia 71-85%
  - Malaise 76-80%
  - N / V 67-79%
  - Headache 19-73%
  - Pale stool 52-58%
  - Fever 18-58%
  - Abd pain 26-54%
  - Arthralgias 6-19%
- Signs
  - Jaundice 40-80%
  - Hepatomegaly 14-78%
  - Hep. tenderness 39-46%
  - Bradycardia 17%
  - Skin rash 14%
  - Splenomegaly 3-13%
  - Lymphadenopathy 4%

Epidemic and sporadic cases of acute hepatitis A

Acute Hepatitis A - Serology

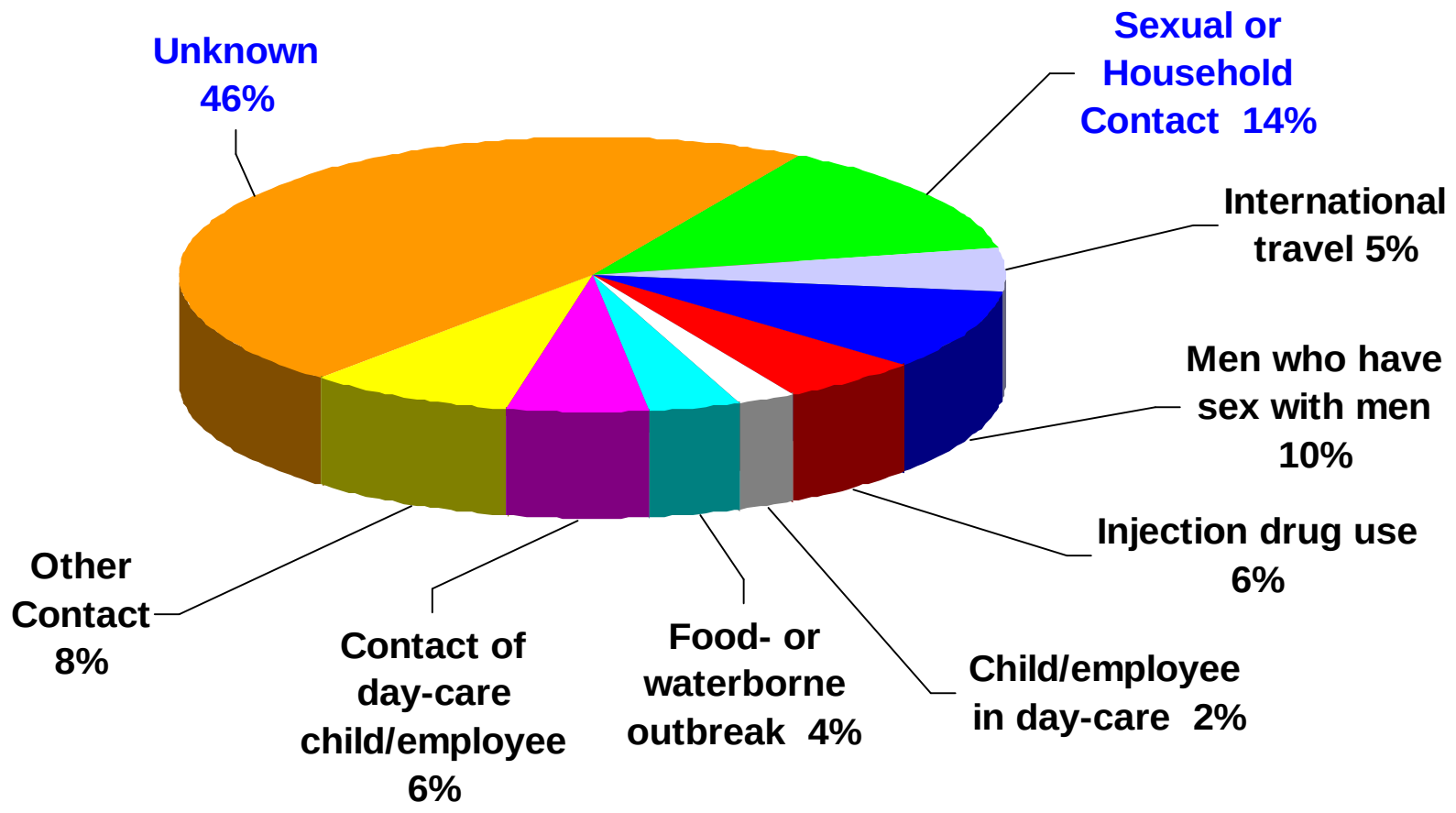
- Detection of specific IgM anti-HAV in single acute phase serum specimen
- IgM anti-HAV remains positive for most patients for 6 to 12 months
- IgM anti-HAV remains positive for up to 12 months in up to 25% of patients and can last 2 years or longer
- IgM anti-HAV has been detected 2--3 weeks after administration of one dose of HepA vaccine in 8%--20% of adults
- Total anti-HAV antibody (IgM plus IgG) results are not clinically helpful unless reflex testing for IgM anti-HAV occurs

Hepatitis A Virus Transmission

- **Fecal-oral**
- **Close personal contact**
  (e.g., household contact, sexual contact, child day care centers)
- **Contaminated food, water**
  (e.g., infected food handlers, raw or undercooked mollusks harvested from contaminated water, contaminated produce [e.g. lettuce, strawberries, green onions or pomegranate seeds])
- **Blood exposure (rare)**
  (e.g., injecting drug use, rarely by transfusion and clotting factor concentrates)

Risk Factors Associated with Reported Hepatitis A,

United States 1990 - 2000

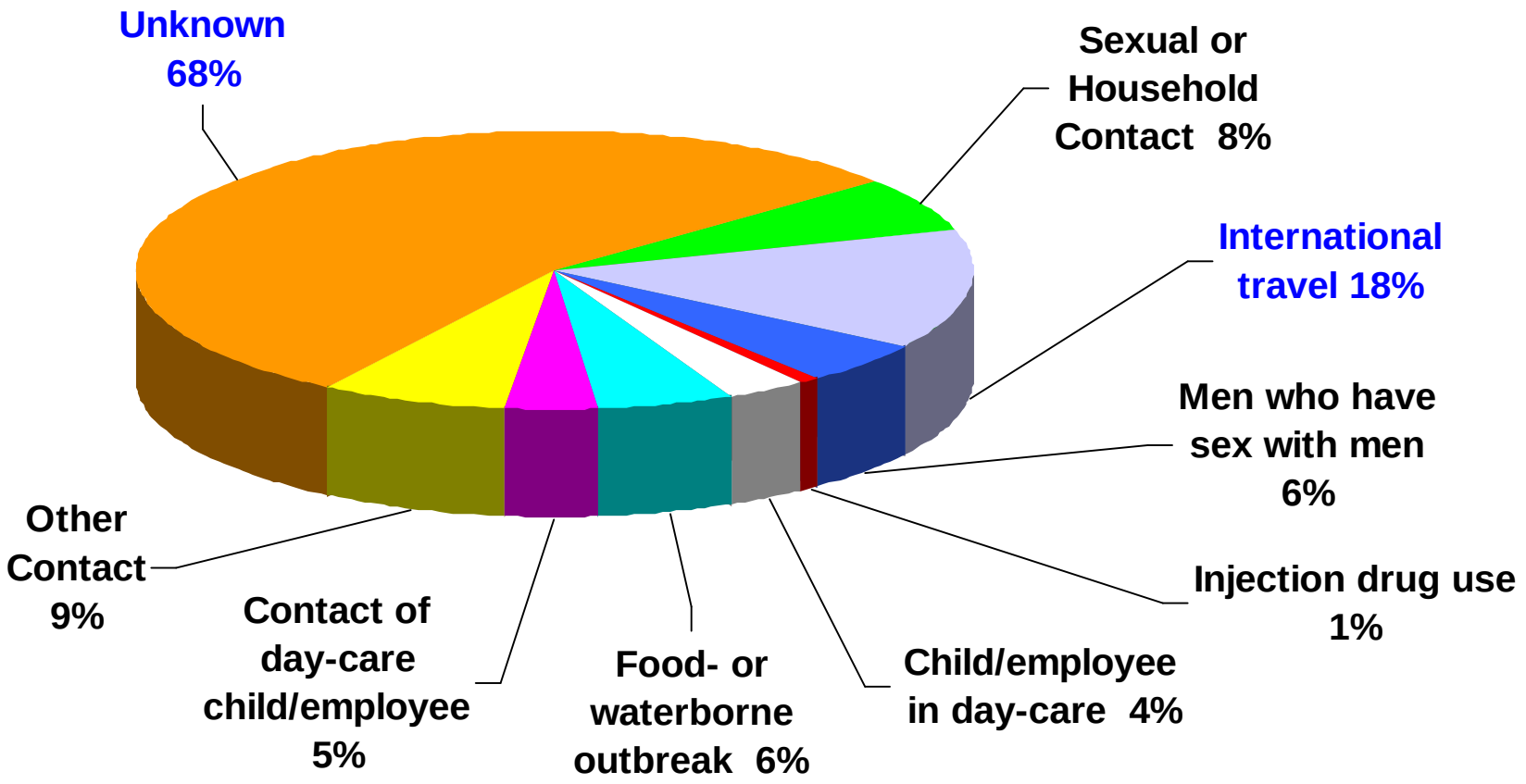


Source: CDC (NNDSS/ VHSP)

Cabinet for Health and Family Services

Risk Factors Associated with Reported Hepatitis A,

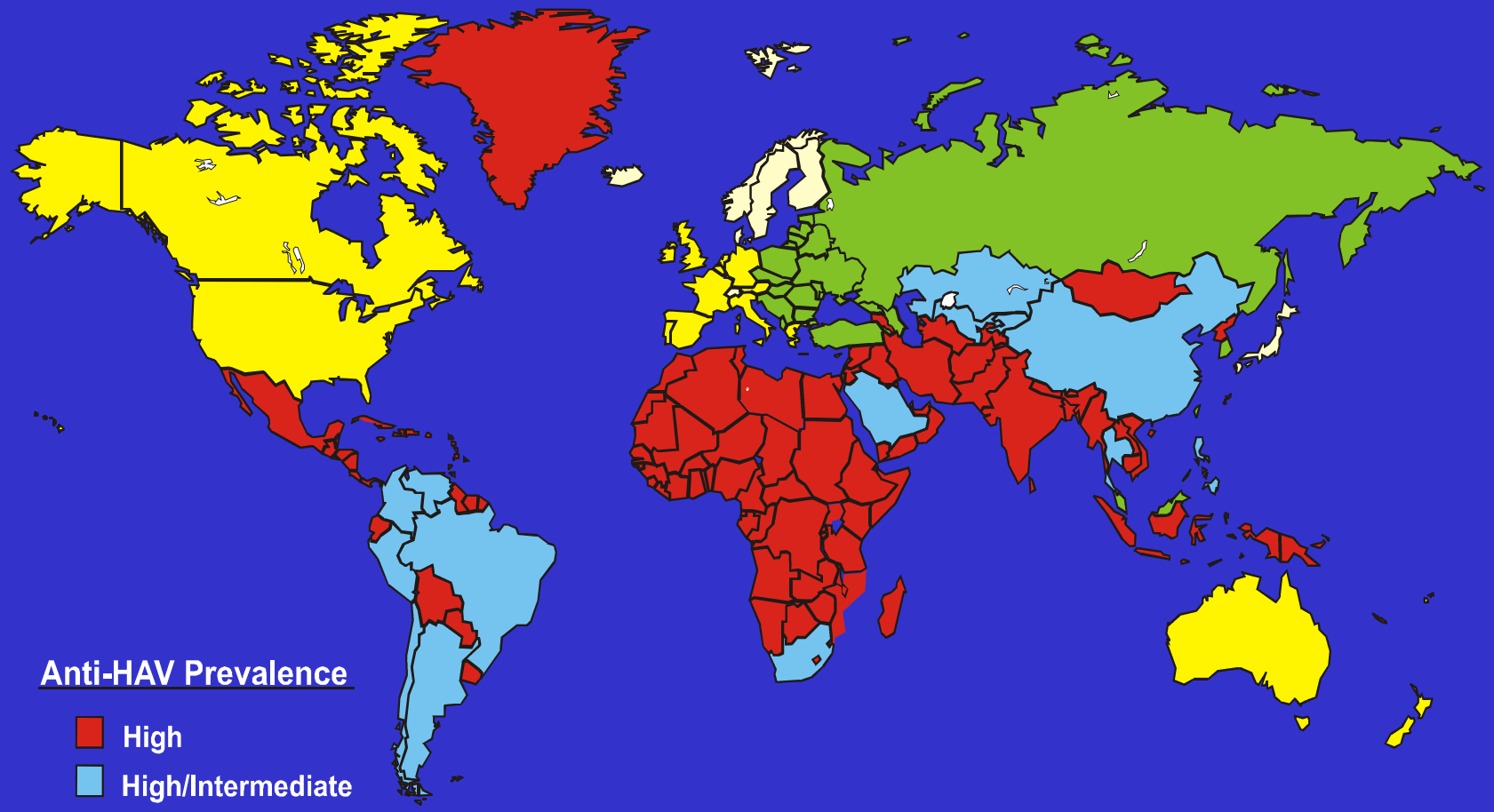
United States 2007



Percentages based on total number of cases for which information about that risk factor was reported – may not total 100%

Kentucky Public Health
Prevent. Promote. Protect.

Geographic Distribution of HAV Infection, 2008

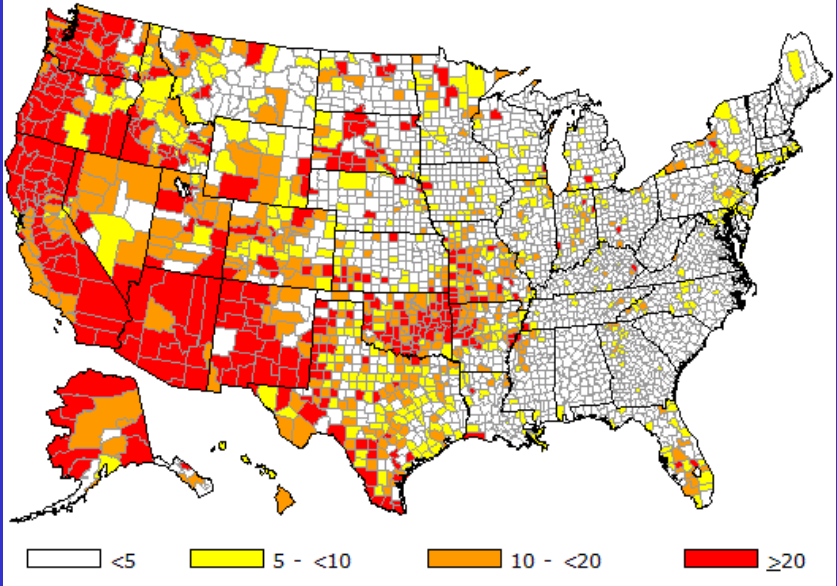


Countries outside the US other than Canada, Australia, New Zealand, Japan, and Western Europe should be considered to have high or intermediate endemicity for hepatitis A virus.

Cabinet for Health and Family Services

Map of Acute HAV Cases – United States

1987 - 1997

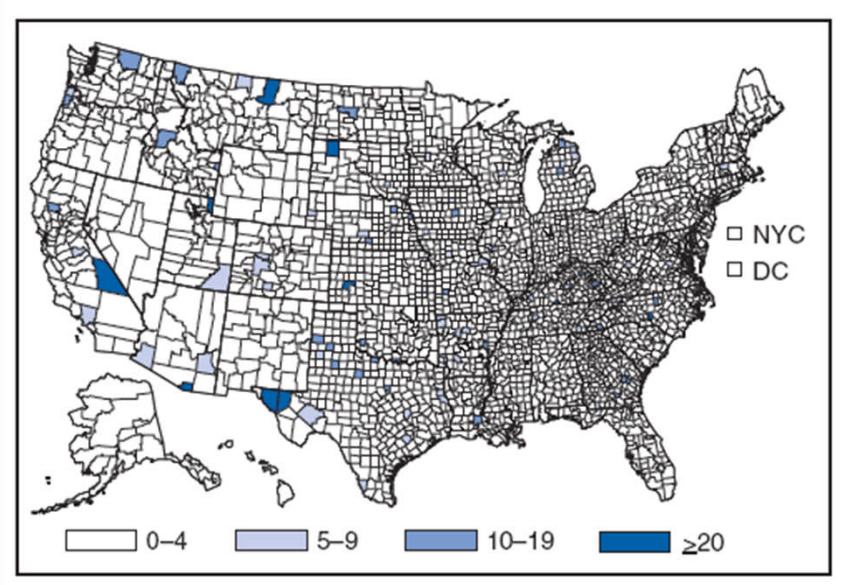


Average reported cases of Hepatitis A per 100,000 population

http://www.cdc.gov/hepatitis/HAV/Historical-USMap.htm

Cabinet for Health and Family Services

2006

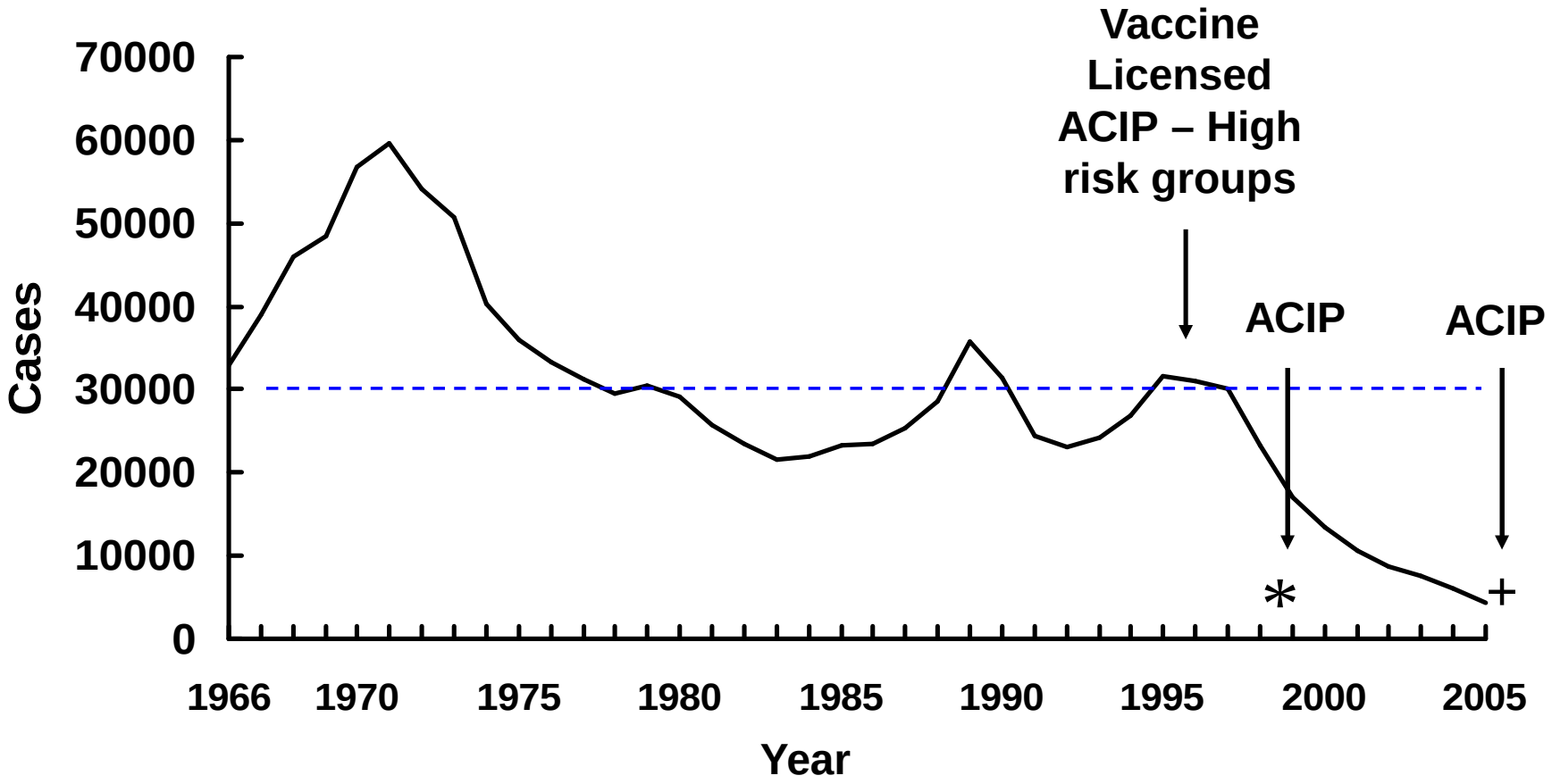


Reported cases of Hepatitis A per 100,000 population

Rates in the West about the same as other US regions

http://www.cdc.gov/mmwr/preview/mmwrhtml/ss5702a1.htm

Hepatitis A - United States, 1966 - 2005*



ACIP – Routine childhood schedule

* 1999 Vaccine – 11 High risk states

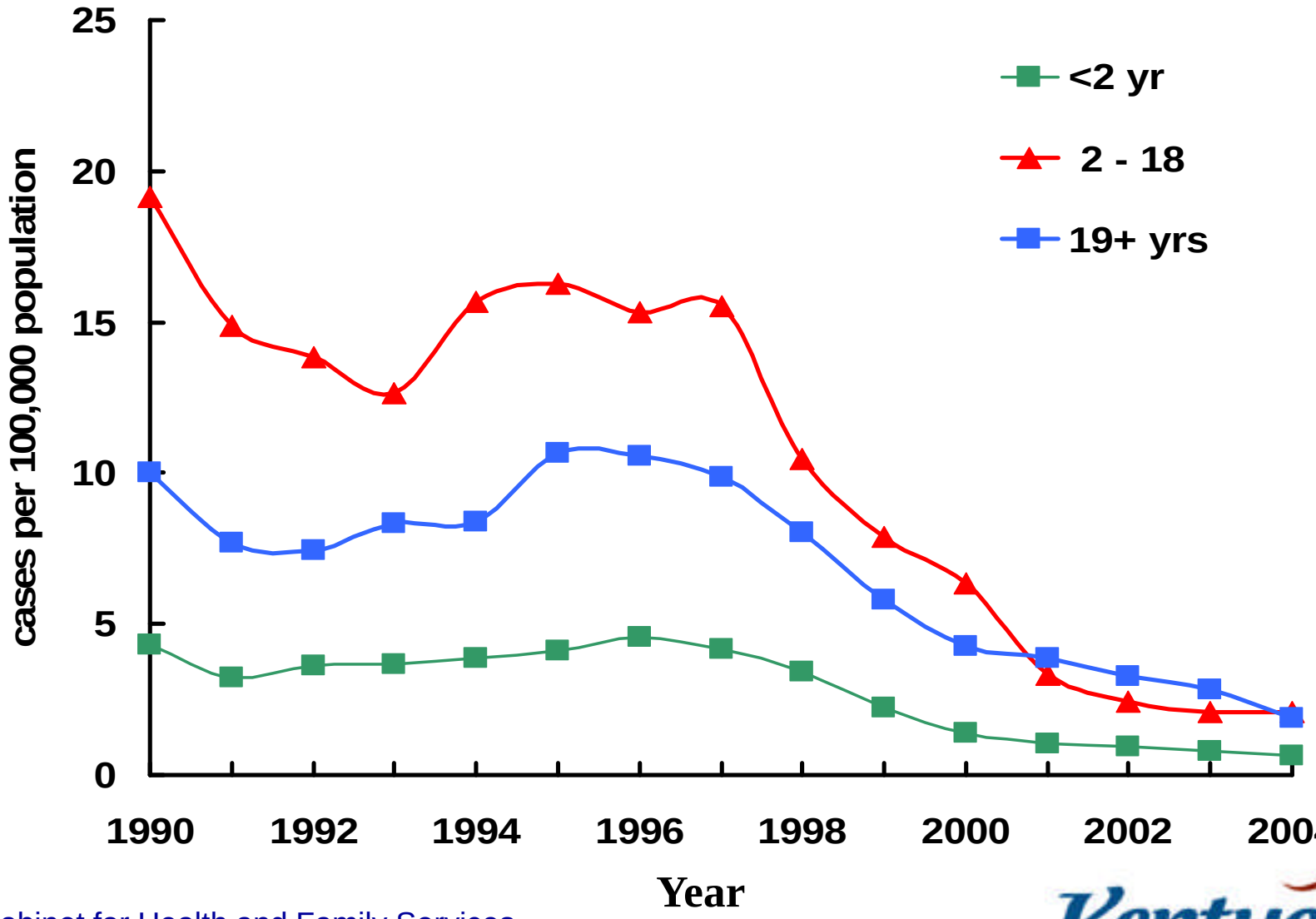
\+ 2006 Vaccine – ACIP schedule

*2005 provisional total

2007 – 2,791 cases reported

2010 – 1,670 cases reported

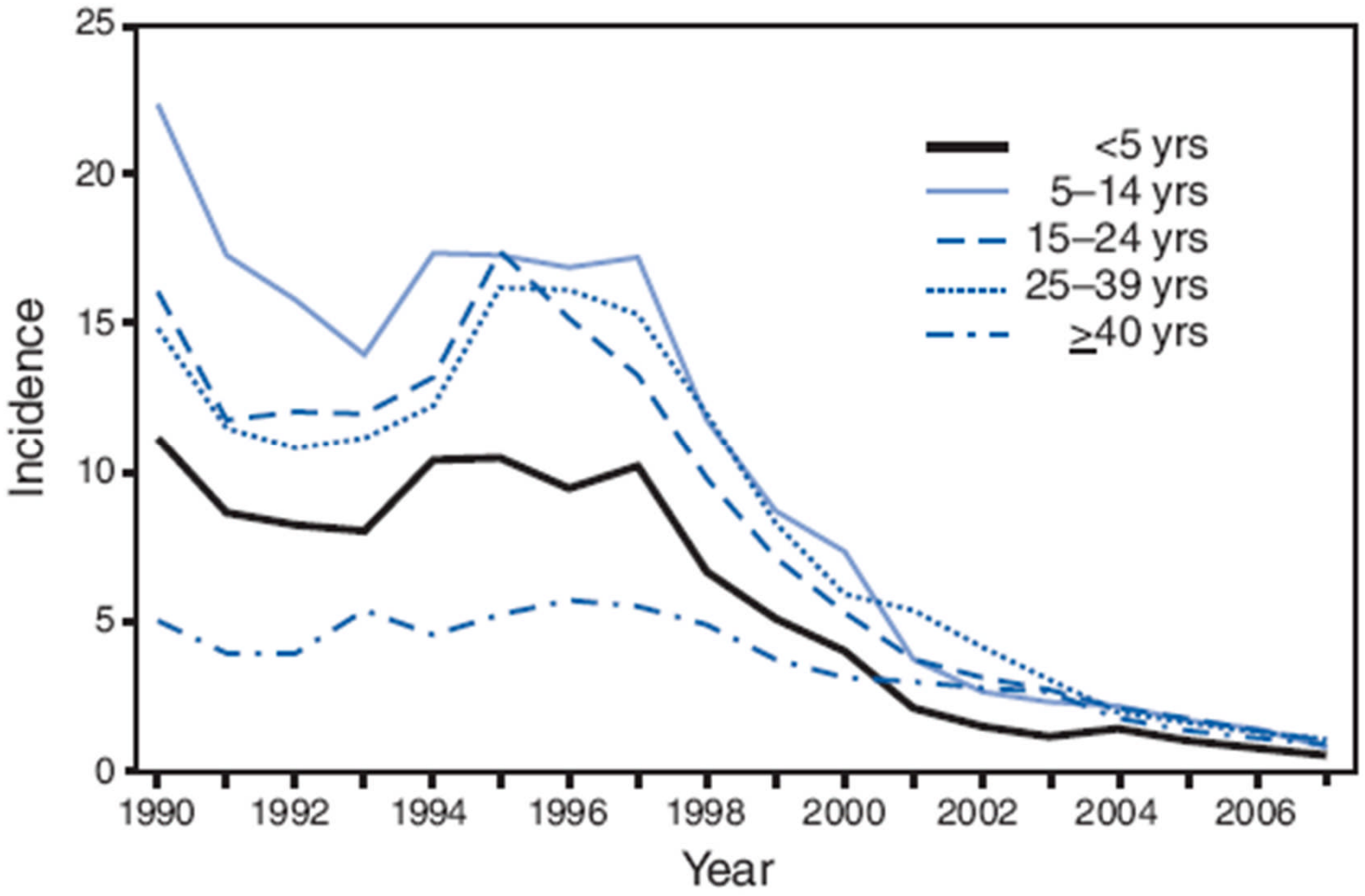
Hepatitis A Incidence By Age Group, 1990 - 2004



Cabinet for Health and Family Services

Kentucky
UNBRIDLED SPIRIT

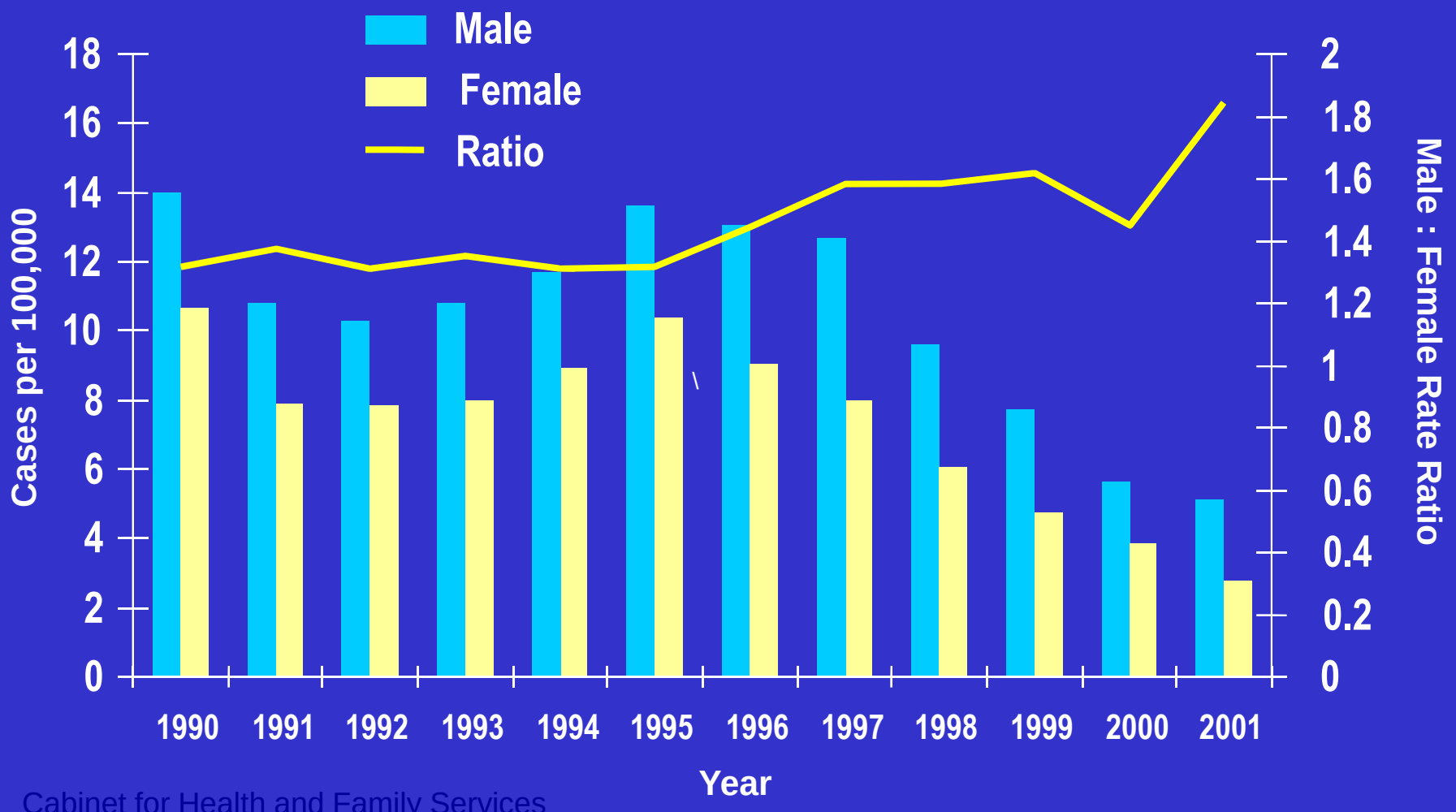
Hepatitis A Incidence By Age Group, 1990 - 2007



Per 100,000 population

Hepatitis A Incidence by Gender,

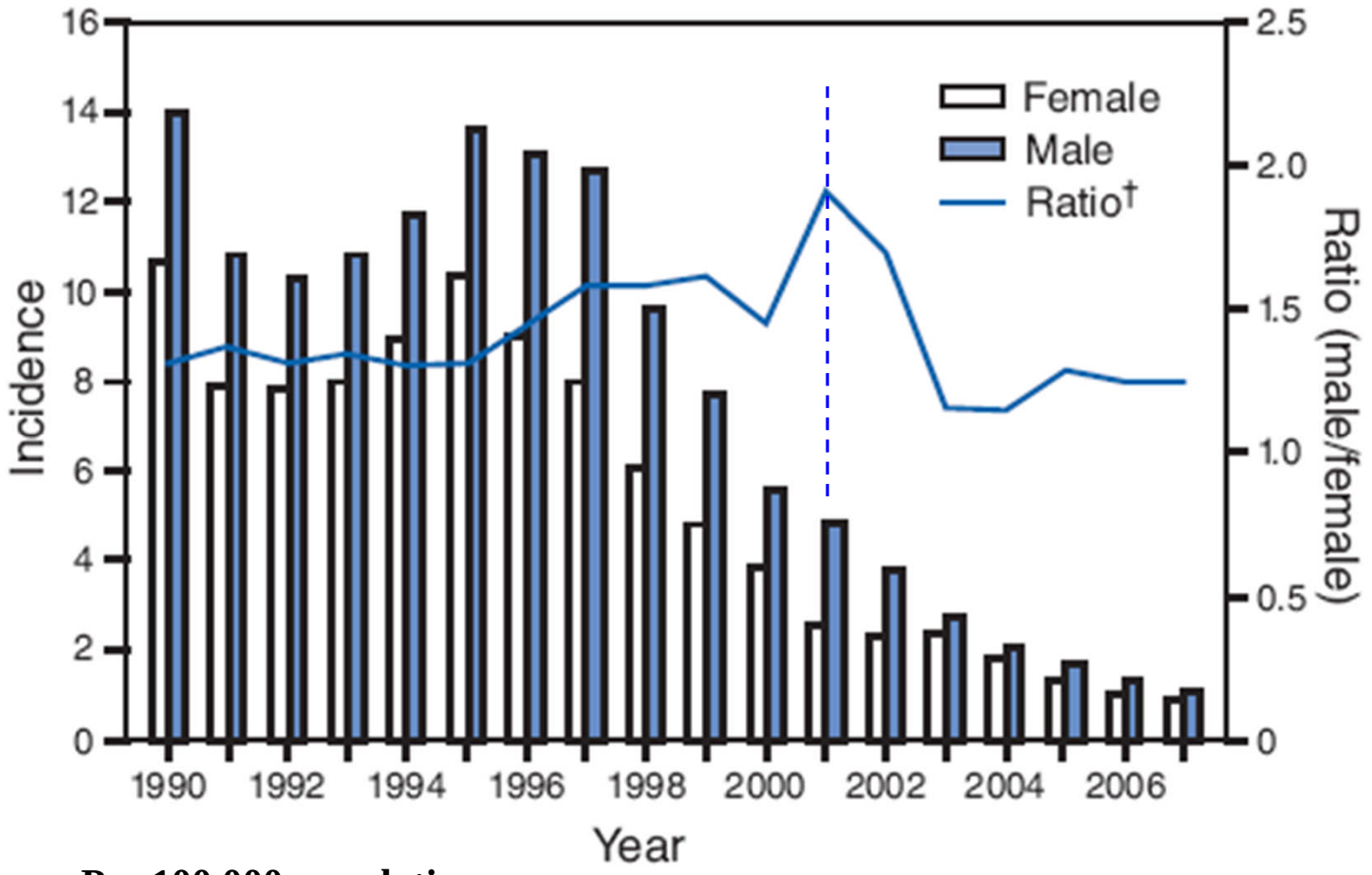
United States, 1990 - 2001



Cabinet for Health and Family Services

Hepatitis A Incidence by Gender,

United States, 1990 - 2007



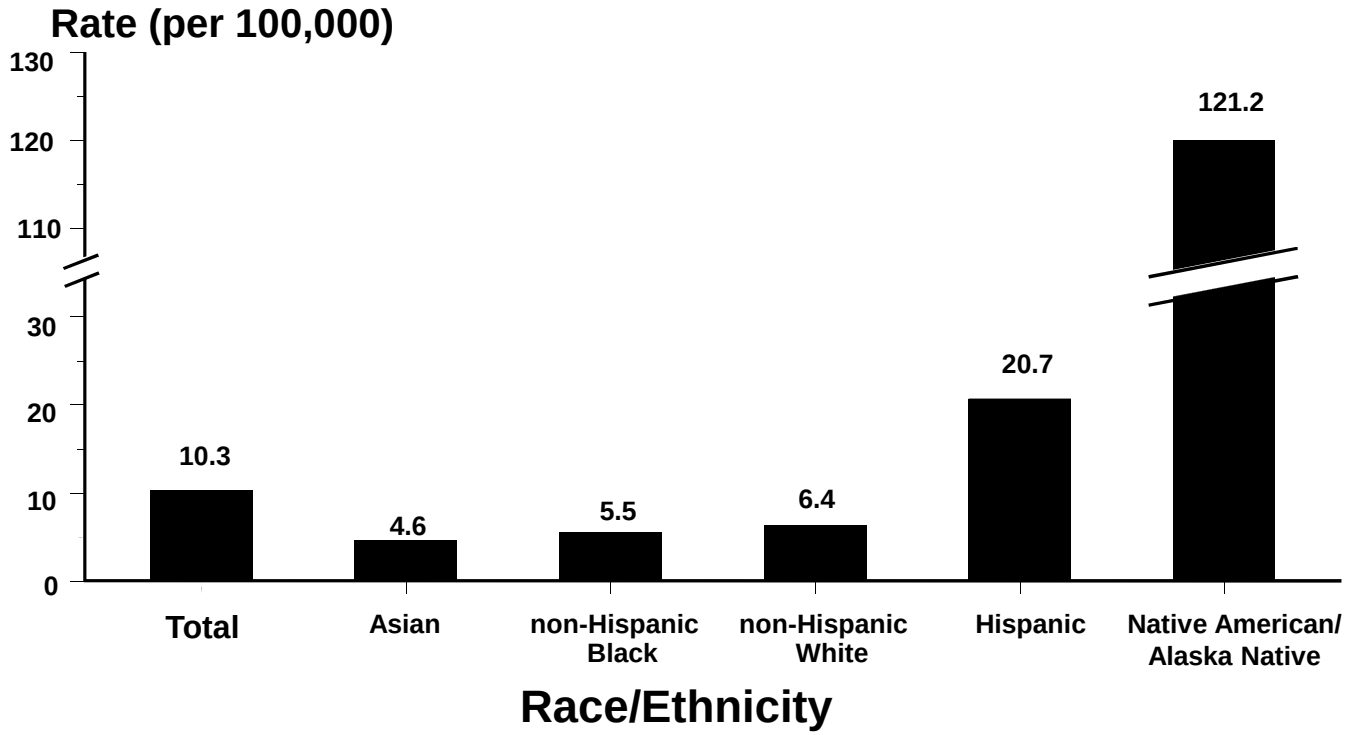
Per 100,000 population

Cabinet for Health and Family Services

Kentucky UNBRIDLED SPIRIT

Hepatitis A Rates,

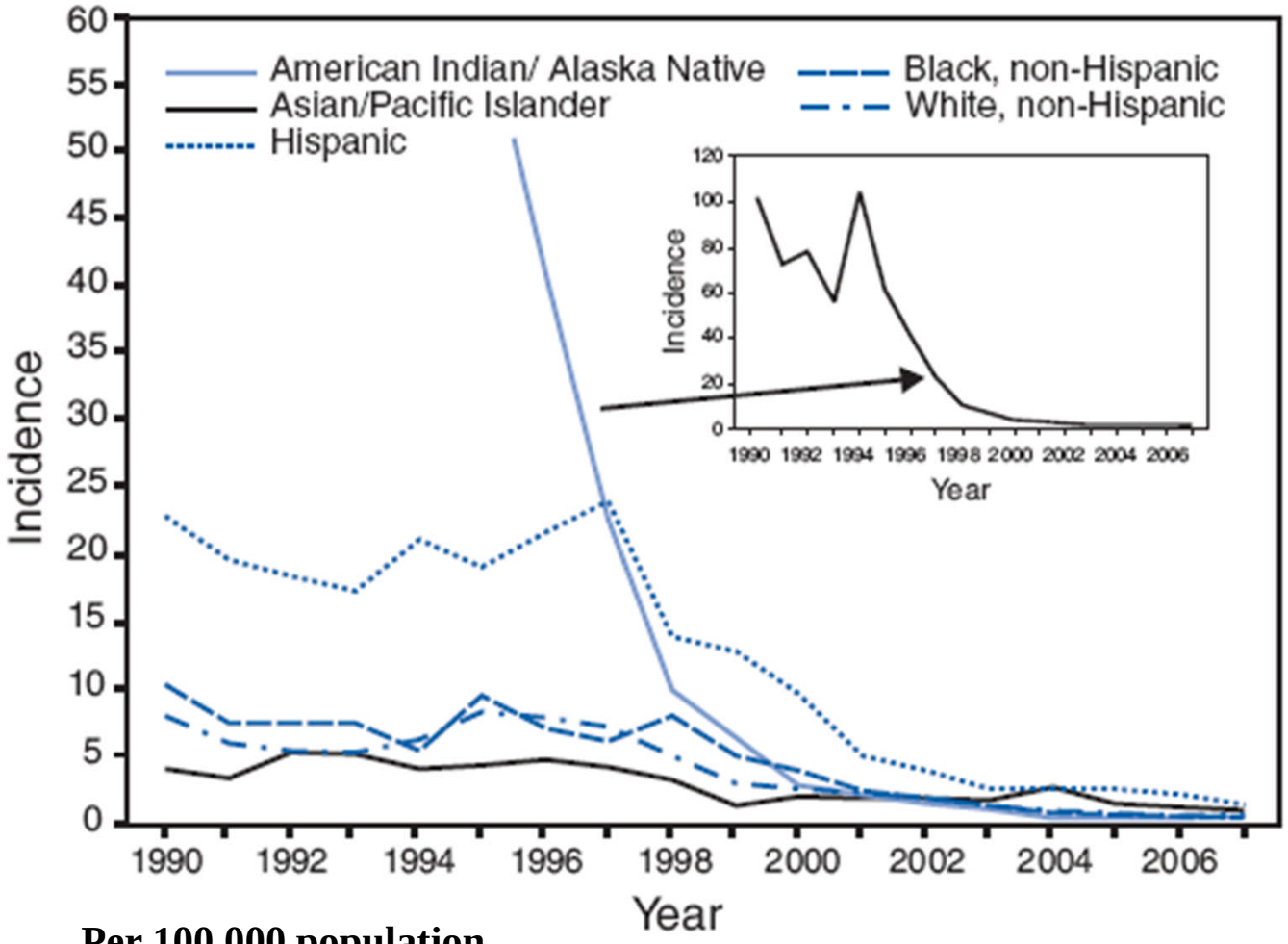
by Race / Ethnicity; 1994



Kentucky UNBRIDLED SPIRIT

Hepatitis A Rates, United States,

by Race / Ethnicity; 1990 - 2007



Per 100,000 population

Prevention of Hepatitis A Infections

- Improved personal hygiene, particularly handwashing
- Provision of safe drinking water
- Proper sanitary waste disposal
- Preexposure immunization
- Postexposure immunization and / or administration of immune globulin

Hepatitis A chapter in Feigin and Cherry's Textbook of Pediatric Infectious Diseases, 7th Ed, 2014

Hepatitis A Vaccines

Single-antigen Vaccines

- Inactivated whole virus
- HAVRIX (GlaxoSmithKline)
- VAQTA (Merck)
- Pediatric and adult formulations
- Licensed for persons aged 12 months and older

Hepatitis A Vaccine Immunogenicity

Single-antigen Vaccines

Adults

- >95% seropositive after one dose
- 100% seropositive after two doses

Children (≥12 months) and Adolescents

- >97% seropositive after one dose
- 100% seropositive after 2 doses

Hepatitis A Vaccines

Schedule for Single-antigen Vaccines

Adults

- 1 dose
- Booster dose 6-18 months after first dose

Children and Adolescents

- 1 dose
- Booster dose 6-18 months after first dose

HEPATITIS A VACCINES

Recommended Dosages of Single-antigen Hepatitis A Vaccines

Vaccine	Age (yrs)	Dose	Volume (mL)	2-Dose Schedule (mos)
HAVRIX ® #	1-18	720 (EL.U.*)	0.5	0, 6-12
	>18	1,440	1.0	0, 6-12
VAQTA ® ##	1-18	25 (U**)	0.5	0, 6-18
	>18	50	1.0	0, 6-18

* EL.U. – Enzyme-linked immunosorbent assay (ELISA) units, ** Units

has 2-phenoxyethanol as a preservative, ## has no preservative

ACIP Recommendations for Routine Pre-exposure

Hepatitis A Vaccination of Children

- All children should receive hepatitis A vaccine at age one year (i.e., 12 through 23 months of age)
- Vaccination should be integrated into the routine childhood vaccination schedule
- Children who are not vaccinated by 2 years of age can be vaccinated at subsequent visits

Hepatitis A Vaccine Recommendations for

Pre-exposure Protection for High Risk Groups

- International travelers
- Close contact with international adoptee from a country with high or intermediate endemicity
- Men who have sex with men
- Persons who use illegal drugs
- Persons who have a clotting-factor disorder
- Persons with occupational risk
  - Persons who work with HAV-infected primates or with HAV in laboratory research
- Persons with chronic liver disease

Hepatitis A Prevention

Recommendations for Pre-exposure Protection for International Travelers (2007 ACIP)

- Susceptive persons traveling to or working in in high- or intermediate- risk countries (e.g. Mexico & South America)
- Give single-antigen hepatitis A vaccine or IG before departure. Single-antigen hepatitis A vaccine, at the age appropriate dose, is preferred over IG.
  - Healthy persons (aged 40 and younger) – one dose of single-antigen hepatitis A vaccine given at any time before departure should be protective
  - Older adults, immunocompromised persons, persons with chronic liver disease or other chronic medical conditions planning to depart to an at-risk area in less than two weeks: give first dose of single antigen hepatitis A vaccine **AND** give IG (0.02 mL/kg) at a separate site

Hepatitis A Prevention

Recommendations for Pre-exposure Protection for International Travelers (2007 ACIP) (continued)

  - Travelers who refuse vaccine, are aged less than 12 months, or who have vaccine contraindications – give a single dose of IG (0.02 mL/kg) for up to 3 months of protection against hepatitis A infection
  - For such travelers whose travel period is expected to be longer than two months, give IG (0.06 mL/kg); repeat the IG administration if the travel period is longer than five months.
- Completion of the hepatitis A vaccine series is necessary for long-term protection

Single-antigen Hepatitis A Vaccine

Recommendations for Selected Occupational Groups

- Healthcare workers: not routinely recommended
- Child care centers: not routinely recommended
- Sewer workers or plumbers: not routinely recommended
- Food handlers: may be considered based on local circumstances

Duration of Protection

After Hepatitis A Vaccination

- Persistence of antibody
  - At least 5-8 years among adults and children
- Efficacy
  - No cases in vaccinated children at 5-6 years of follow-up
- Mathematical models of antibody decline suggest protective antibody levels persist for at least 20 years
- Other mechanisms, such as cellular memory, may contribute

Pre-Vaccination Testing

- Considerations for cost vs. benefit:
  - cost of vaccine
  - cost of serologic testing (including visit)
  - prevalence of hepatitis A infection
  - impact on compliance with vaccination
- Likely to be cost-effective for:
  - persons born in high endemic areas
  - Older U.S. born adults
  - Older adolescents and young adults in certain groups (e.g., Native Americans, Alaska Natives, Hispanics, IDUs)

POST-VACCINATION TESTING

Not Recommended for Single-antigen Hepatitis A Vaccines

- High response rate among vaccinees
- Commercially available assay not sensitive enough to detect lower (protective) levels of vaccine-induced antibody

Hepatitis A Vaccines

Combination Vaccines

- TWINRIX® (GlaxoSmithKline)
- Combination of inactivated whole HAV (pediatric HAVRIX®, 720 EL.U.) and hepatitis B surface antigen (adult ENGERIX-B®, 20 mcg HBsAg)
- Licensed for persons 18 years of age and older
- Licensed by FDA in 2001 for 3-dose schedule
- FDA approved 4-dose accelerated dosing schedule in 2007
- Indicated for persons at risk for exposure to both HAV and hepatitis B viruses (see PHPR Immunization chapter)
- **Should not be used in PEP for close contacts to acute hepatitis A infection**

HEPATITIS A VACCINES

Recommended Dosages of Hepatitis A / Hepatitis B Combination Vaccine

Vaccine	Age (yrs)	Dose	Volume (mL)	3-Dose Schedule (mos)	4-Dose Schedule (days)
TWINRIX ® #	18	720 (EL.U.*)	1.0	0	0
	and	20 mcg HBsAg	1.0	1	7
	older		1.0	6	21 to 30
Booster, 4-dose schedule (only)			1.0		12 Months

* EL.U. – Enzyme-linked immunosorbent assay (ELISA) units, HAV

has no preservatives

Hepatitis A - Postexposure Prophylaxis (PEP)

- Persons exposed to HAV who have no prior history of hepatitis A vaccination: Give single dose of single-antigen hepatitis A vaccine or immune globulin (IG, 0.02-mL/kg IM) as soon as possible (2007 ACIP recommendation)
  - Healthy persons aged 12 months through 40 years, single-antigen hepatitis A vaccine, at the age appropriate dose, is preferred over IG
  - Children younger than 12 months – give IG
  - Adults older than 40 years, preferable give IG. Use single-antigen hepatitis A vaccine if IG is unavailable.
  - Immunocompromised persons, persons with chronic liver disease diagnosed, or persons for whom vaccine is contraindicated – give IG
- Persons given IG for whom vaccine is also recommended can be given a dose of vaccine simultaneously with IG
- Persons given vaccine should complete the series

Acute Hepatitis A – Surveillance Case Definition

- **2012, Clinical criteria of an acute illness with:**
  - Discrete onset of any sign and symptom consistent with acute viral hepatitis (e.g., fever, headache, malaise, fatigue, anorexia, nausea, vomiting, diarrhea, and abdominal pain), **AND**
  - Either jaundice or elevated serum aminotransferase levels
- **Laboratory criteria**
  - IgM antibody to hepatitis A virus (IgM anti-HAV) positive
- **Case Classification** - Confirmed
  - **A case that meets the clinical case definition and is laboratory confirmed, OR**
  - A case that meets the clinical case definition and occurs in a person who has an epidemiologic link with a person who has laboratory-confirmed hepatitis A (i.e., household or sexual contact with an infected person during the 15-50 days before the onset of symptoms).

Investigation of a case

- **Public health – urgent event**, team response
  - CONFIRM DIAGNOSIS IN INDEX CASE
  - Identify close contacts (e.g. household, sexual)
    - Limited timeline (i.e. 14 days of last exposure) to provide postexposure prophylaxis (PEP)
    - Secondary attack rates in households – 15% to 30%
    - No evidence on efficacy of PEP when given two weeks for more after last HAV exposure
    - Maintain surveillance for 50 days after last exposure
  - Infection control
    - Handwashing
    - Contact precautions for first two weeks of illness, but no more than one week after onset of jaundice

Investigation – Special circumstances

- Food handler with acute hepatitis A infection
  - Environmental inspection of establishment
  - Environmental cleaning – 1:100 dilution chlorine bleach for surfaces
  - PEP (i.e. single-antigen hepatitis A vaccine or IG) should be give to other food handlers in same establishment
  - Higher risk of HAV exposure to patrons in infectious period if:
    - Food handler had diarrhea
    - Food handler had deficiencies in personal hygiene
    - Food handler prepared foods not heated
    - Food handler directly handled cooked foods
  - Any response with single-antigen hepatitis A vaccine or IG has to be completed within 2 weeks of last exposure
  - Maintain surveillance for 50 days after last exposure

Investigation – Special circumstances

- Day care centers; child care centers – Acute hepatitis A infections
  - PEP (i.e. Hepatitis A vaccine or IG) is indicated for ALL PREVIOUSLY UNVACCINATED adult staff and attendees when:
    - One or more cases of hepatitis A are recognized in children or adult staff
    - Two or more households of attendees have cases
    - Only treat classroom contacts of index case in centers that have no children in diapers
  - Outbreak (three or more families have hepatitis A cases), treat members of households with attendees in diapers

Kentucky Public Health
Prevent. Promote. Protect.

Questions ?